REMARKS

Status of the Claims

Claims 9, 15, 16, 40-46 and 48 are in the application.

Claims 9, 15, 16, 40-46 and 48 were rejected.

Claims 15 and 43 have been amended. Claim 48 has been canceled without prejudice.

Upon entry of this amendment, claims 9, 15, 16, and 40-46 will be pending.

Summary of the Amendment

Claims 15 and 43 have been amended solely in order to further prosecution and the amendment does not change the scope of the claim for the reasons stated below. No new matter has been added.

Interview Summary

Applicants thank the Examiner for reissuing the present Office Action indicating that it is non-Final in view of our telephone conversation on July 23, 2009.

Double Patenting

The Office alleges that should claim 46 be found allowable, claim 48 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. The Office alleges that claims 46 and 48 would have the same scope if they were both allowed. Applicants have canceled claim 48 rendering obviating this potential objection. Accordingly, Applicants respectfully request that the double patenting rejection be withdrawn.

Claim Rejection Under 35 U.S.C. § 112, second paragraph

Claims 15 and 43 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office alleges that claims 15 and 43 each recite the term "said DNA" without sufficient antecedent basis for the term. Applicants note that claims 15 and 43 do not just recite "said DNA" but the whole term is "said DNA molecule." Applicants respectfully point out that one of skill in the art reading claims 15 and 43 would have understood

and known that the phrase "said DNA molecule" was referring to is the same "free DNA molecule" recited throughout the claim. The Office has provided no evidence as to why the omission of the term "free" changed one of skill in the art's understanding of the claim such that one of skill in the art would not have known the metes and bounds of the claims. Although the previous claim was clearly definite because one of skill in the art would have understood the claims, Applicants have amended the claims, solely in order to further prosecution, to recite "said free DNA molecule."

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Claim Rejections – 35 Under 35 U.S.C. § 103

Claims 9, 15-16, 40-46, and 48 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of:

1. U.S. Patent Application Publication 2004/0063652 (hereinafter "Jolly");
2. Stacey *et al.*, *Journal of Immunology* 157:2116-22 (1996) (hereinafter "Stacey");
3. Kataoka *et al.*, *J. Biol. Chem.*, 272(29):18209-15 (1997);
4. U.S. Patent No. 5,783,567, (hereinafter "Hedley");
5. Samlowski *et al*, *Regional Immunology*, 1(1):41-55 (1988);
6. U.S. Patent No. 5,763,416;
7. Roitt *et al.*, *Immunology*, Published by Gower Medical Publishing, Ltd., Lond, Engalnd, pp. 1-1 to 1-6, 2-10 to 2-13, and 3-1 to 3-9; (1985), (hereinafter "Roitt");
8. Yamanaka *et al.*, *Avian Diseases* 37(2):459-466 (Abstract Only) (1993);
9. Cantini *et al.*, *Journal of Neuropathology and Experimental Neurology*, 54(1):121-28 (1995) (hereinafter "Cantini);
10. Kadir *et al* (1992), *International Journal of Clinical Pharmacology, Therapy, and Toxicology,* 30 (1):374-382 (Abstract Only) (hereinafter "Kadir");

11. Gopalakrishnakone *et al*. Toxicon: the Official Journal of the International Society of Toxicology, 22(1) 85-98 (1984) (hereinafter "Gopalakrishnakone"; and

12. Beresford *et al*., British Journal of Pharmacology, 12: 107-114 (1957) (hereinafter "Beresford").

The Office cites Roitt in an attempt to demonstrate the one of skill in the art would have known that macrophages will drain to a lymph node. The Office also cites Yamanka, Cantini, Kadir, Gopalakrishnakone and Beresford to allegedly demonstrate that "as far back as 1957, it was well known that macrophages respond to tissue damage in muscle by migrating to the damage site." Applicants have not argued that one of skill in the art would not have known that macrophages drain to lymph nodes. Applicants have previously argued that the Office has not satisfied its burden in demonstrating that the presently claimed invention is *prima facie* obvious. The Office alleges that

> It is clear that Jolly teaches transfection of macrophages *in vivo* with plasmids, Hedley and Samlowski teaches the transformation of the macrophages will lead to transfected macrophages in the draining lymphnodes, Roitt demonstrates that the Artisan understand the circulation of Macrophages and they circulate through all tissues, Yamanaka, Cantini, Kadir, Gopalakrishnakone, and Beresford demonstrate that macrophages are specifically attracted to the site of muscle tissue damage, and Kataoka and Bonadio teach the require signals for expression of a gene in macrophages.

(Office Action, page 7). The Office alleges that the "Artisan would be motivated to choose a site local to the lymph node target…because macrophages were known to drain to local lymph nodes." (Office Action, page 8). Applicants respectfully disagree.

The present rejection arises out of the withdrawal of a previous obviousness rejection. The previous rejection was withdrawn after Applicants filed a Request for a PreAppeal Conference Review. The Office essentially alleges that the rejection was withdrawn not because the claims are not obvious, but because the only deficiency in the rejection was that there were not references of record showing that macrophages are present and attracted to tissue damage

sites and the previous rejection did not make clear that these macrophages are part of the immune response and drain to local lymph nodes.

The presently claimed invention is not *prima facie* obvious. Applicants argument has not focused on whether macrophages are present or whether macrophages drain to lymph nodes. Instead, Applicants' contention that the presently claimed invention is not obvious because the references do not support a *prima facie* obviousness rejection, many of the references teach away from the presently claimed invention, and the combination of the references fails to demonstrate that one of skill in the art would have had a reasonable expectation of success. Finding twelve references instead of the previously cited five does not cure these deficiencies. Contrary to helping the obviousness rejection, many of the newly cited references teach way and demonstrate that there is no reasonable expectation of success. Therefore, the Office has still not carried its burden to show that the presently claimed invention is *prima facie* obvious.

The Office alleges that Jolly teaches the use of plasmids to effect the transformation of macrophage cells to effect killing and for the general secretion of proteins that block pathogenic interactions local to cell. The Office also alleges that Jolly discuses that having a vector expressed in a target lymphnode is desired.

The claimed invention is not obvious. The cited art has not been interpreted accurately by the Office. Proper consideration of the art does not establish a *prima facie* case of obviousness. Moreover, there is nothing within the amorphous "combined knowledge" that would have led to the combination of the claimed invention. Finally, those skilled in the art viewing the art would not recognize the benefits achieved by the claimed invention.

The pending claims are not obvious because the cited references do not yield the present invention, teach away from the pending claims, and even if the references are combined to yield the present invention do not give rise to a reasonable expectation of success.

None of the references discuss the step of identifying a lymphnode as a target for delivery of a protein and locating a site that is proximal to the lymphnode. None of the references disclose that upon administration of the free DNA to an individual, the free DNA is

taken up by the macrophage cell and the macrophage then drains to the lymphnode. In contrast, many of the references cited by the Office teach away from these elements.

The Jolly references discloses expressing a protein in a macrophage by introducing a vector that comprises the protein's nucleic acid coding sequence under the control of a macrophage specific promoter into a macrophage. Jolly, however, does not disclose how to administer the vector to the macrophage. Additionally, the Jolly reference fails to disclose the step of identifying a lymph node and the delivery of a protein to the lymph node by administering DNA to a site located on the individual's body that is proximal to the lymphnode.

The remaining references to do not make up the deficiencies of Jolly.

The Hedley reference teaches away from the use of free DNA and intramuscular administration. The Hedley references discusses microparticles that are effective for delivering DNA to be taken up by phagocytic cells. Microparticles are not free DNA.

With reference to macrophages, the Hedley reference expressly teaches away from using intramuscular injection. The Hedley reference discloses a specific method for delivering DNA that is encapsulated in microparticles to cells in the lymph node, stating: "one can target, via ***subcutaneous injection***, take up by the phagocytic cells of the draining lymph nodes." (Col. 8, lines 22-24, emphasis added). A careful reading of the Hedley reference reveals that the microparticles comprising DNA are injected subcutaneously and are taken up by cells in the lymph nodes. The Hedley reference teaches intradermal administration of microparticles comprising DNA to target dendritic cells in the skin. (Col. 8, lines 25-27). The Hedley reference does not teach intramuscular administration for delivery to macrophage cells which migrate to the lymph node. Rather, one skilled in the art reading the Hedley reference would conclude that subcutaneous delivery of microparticles is required to deliver the DNA to macrophage in the lymph nodes.

The Office attempts to cure the deficiencies between of Hedley and Jolly by citing Stacey. The Office states:

> [W]ith regard to the possibility that Jolly is randomly teaching the use of plasmid and it is not enabled, Stacey teaches that plasmids are taken up by macrophages and transgenes are expressed (*e.g.*

> Figure 6). Hence, the Artisan knows specifically that macrophages will pick up plasmids and express transgenes therein.

(Office Action, pages 5-6). The Stacey reference fails to teach or suggest that a DNA molecule will be taken up by a macrophage *in vivo*. Stacey describes experiments that are *in vitro*. Stacey fails to show even a single experiment or result demonstrating that macrophages *in vivo* can take up DNA and/or deliver the free DNA molecule to a lymph node. The Office's reference to Figure 6 exemplifies this fact. Stacey's Figure 6 shows the results of an experiment where a luciferase plasmid had to be incubated at a high concentration to detect internalization of the plasmid. Stacey states that "The initial high concentration incubation **was necessary** to get good levels of expression." (Stacey, p. 2120). Furthermore, Stacey casts doubt as to whether the result and mechanism they describe is even what occurs *in vivo*. "In the **normal** *in vivo* situation…[a] recognition system for the DNA…remain[s] to be established." (Stacey, p. 2121). One of skill in the art reading this concluding paragraph and the use of the term "normal *in vivo*" would understand that the experiments do not provide insight as to what will occur *in vivo*.

There is a significant difference between incubating a cell with a plasmid and seeing internalization of a plasmid in a tissue culture dish and having a reasonable expectation of success that a free DNA molecule will be taken up by a macrophage cell *in vivo* and delivered to a lymph node. The Stacey reference fails to show that the presently claimed method is even possible let alone that one of skill in the art would have a reasonable expectation of success with respect to the presently claimed invention. None of the other references cure the deficiencies cited above.

In addition to teaching away from using intramuscular injection, the Hedley reference also teaches away from using free DNA. The Hedley reference in its examples emphasizes the effectiveness of using microparticles to deliver DNA and how micro particle encapsulated DNA is superior to using other forms of DNA including naked DNA. The Hedley references teaches one of skill in the art to use microparticles to deliver a DNA molecule instead of using naked DNA (see, for example, Hedley, Col. 18, lines 35-49). One of skill in the art, considering the Hedley reference in its entirety, would use microparticles as opposed to free DNA because of the Hedley reference teaches the relative ineffectiveness of using free DNA.

One skilled in the art would not combine the Hedley reference with the combination of the other references. As noted above, Jolly does not disclose elements of the claims and the combination of the remaining references fail to make up for the deficiencies in Jolly. Thus, there is no *prima facie* case of obviousness.

In addition, if one skilled in the art combined the teachings of Hedley with Jolly, and the other references, the benefits of the invention would not be expected. One of skill in the art would not have expected that intramuscular injection would result in delivery a protein to a lymph node nor would they expect that free DNA could be used to deliver a protein to a lymph node.

None of the references cited indicate that intramuscular injection of free DNA would result in the delivery of free DNA to a macrophage, which would then migrate to the lymph nodes. The combination of references simply does not provide any indication that such a result would be expected.

Likewise, the combination of references does not provide any indication that free DNA could be used to deliver DNA to macrophage which then migrate to the lymph nodes. The present specification states, "surprisingly the [free] DNA is not degraded in this process." (Specification, page 39, lines 5-6).

As discussed above, the Jolly reference only refers to delivering a DNA molecule to a macrophage but does not teach how to do this. The Hedley reference specifies delivering DNA by using microparticles and that delivery of the microparticles to cells in the lymph nodes is achieved via subcutaneous injection. The other art cited by the Office does not give rise to an expectation of success for one of skill in the art. Therefore, based upon the cited prior art it would have been unexpected that one of skill in the art could have.

In attempt to cure these deficiencies the Office cites, in part, Kadir, Beresford, Gopalakrishnakone and Cantini. However, these reference rather than curing the defects in the present rejection the references support Applicants' position that the presently claimed invention is not obvious.

For example, Kadir also does not teach or suggest using a free DNA molecule to deliver a protein to a lymph node. Kadir's abstract (the only part of Kadir that was cited) discusses the tissue reaction after intramuscular injection of liposomes in mice. Kadir does not discuss injecting a free DNA molecule nor whether macrophages can internalize free DNA and effectively deliver them to a lymph node. In contrast to teaching the administration of a free DNA molecule, Kadir teaches away from the use of a free DNA molecule. Kadir clearly disparages the use of free forms of a molecule, that is a molecule that is not encapsulated by a liposome. Kadir states that when the agent Novaminsulfon (NS) was injected intramuscularly

> ***in free form is a strongly irritating drug, causing hemorrhage, cell necrosis, inflammatory reactions and eventually fibrosis.*** However, NS being encapsulated in liposomes was hardly more irritating than liposomes alone. The same was true for liposome-encapsulated chloroquine and free chloroquine.

(Kadir, Abstract, emphasis added). One of skill in the art reading Kadir would understand that a form that is not encapsulated (free form) can cause cell necrosis, hemorrhage or fibrosis. These side effects of a free form would discourage one from using the free form of the agent. Therefore, the Kadir reference not only discourages a free form but disparages a free form because of the severe side effects that result when a free form is used. These issues cannot be ignored when analyzing a reference for what it teaches. Accordingly, Kadir teaches away from the presently claimed invention.

Additionally, the citation of Gopalakrishnakone has no relevance to the presently claimed method. Gopalakrishnakone discusses cellular and mitochondrial changes induced in the structure of murine skeletal muscle by crotoxin, a neurotoxic phospholipase A2 complex. Gopalakrishnakone discusses observations after a neurotoxin is injected into the muscle of a mouse. Gopalakrishnakone does not discuss what would happen after a free DNA molecule might be injected intramuscularly into a mouse. Gopalakrishnakone's only connection with the presently claimed invention is tangential at best. Gopalakrishnakone discusses that when a sublethal dose of the toxin is used macrophages invade the area. Gopalakrishnakone does not state that the macrophages would pick up or internalize DNA and deliver them to lymph nodes.

Cantini also fails to cure the deficiencies of the present rejection. Like the Stacey reference, each and every experiment in Cantini is *in vitro* (i.e. in a tissue culture dish). Cantini cannot be used alone or in combination to show that there was a reasonable expectation of success because of the known differences between *in vitro* and *in vivo* systems. Cantini fails to even discuss what would happen if a free DNA molecule were administered *in vivo*. Furthermore, Cantini does not discuss or even suggest what would happen with a free DNA molecule.

Furthermore, Beresford fails to cure the deficiencies cited above, and in contrast support Applicants' argument that there was no reasonable expectation of success. Beresford discusses local effects and mechanism of absorption of iron preparations administered intramuscularly. Beresford fails to discuss any effects on free DNA molecule absorption. This fact alone would be sufficient to show that Beresford does not provide the necessary facts to support a finding that there is a reasonable expectation of success. Beresford, however, goes one step further stating that "The persistence of iron-laden macrophages in undiminished number in the stroma up to three months after the injection suggest that this iron may be ***permanently fixed***." (Beresford, p. 113, right column, last full paragraph, emphasis added). Therefore, the iron that is taken up by the macrophages is not released into the lymph system and would not be delivered to the lymph node. Extrapolating this to a DNA molecule, which is what the Office has done by citing this reference, would mean that the DNA molecule would be permanently fixed in the stroma and never delivered to the lymph node. Accordingly, one of skill in the art would not have had a reasonable expectation of success when it comes to delivering a free DNA molecule to a lymph node because according to Beresford molecules taken up by macrophages after muscle damage are fixed in the stroma. As with the other references, the Office cannot read the reference for one element without reading the reference as a whole and as one of skill in the art would interpret it.

Prior to the present invention it was not known or obvious that one could deliver a protein to a lymph node by the method described in the pending claims. Here, applicants have shown that DNA injected intramuscularly is taken up by macrophage, which then travel to the lymph node, whereupon the DNA is expressed to effectively deliver the protein to the lymph

node. Applicants have shown that free DNA directly injected into an individual remains intact and functional such that when taken up by macrophage which travel to the lymph node, the DNA can be expressed to effectively deliver the protein to the lymph node. Those skilled in the art would not have expected these beneficial aspects in view of the combination of references.

In anticipation of an appeal, the Office generally argues that because the methods described in Jolly and Hedley and the knowledge of the other references was known that one of skill in the art could have derived the present invention. However, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some ***articulated reasoning*** with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 127 S. Ct. 1727, 1741 (2007). The Office has not put forward any articulated reasoning with some rational underpinning to support its legal conclusion of obviousness. The Office's only claim is that there are references that discuss macrophage specific expression; that microparticles can be taken up by macrophages via subcutaneous injection; that muscle damage leads to macrophage invasion; and macrophages drain to lymph nodes. The Office, however, has failed to articulate a reason why one of skill in the art would have extrapolated any of these methods to those to derive what is now claimed. Therefore, the claims are nonobvious because the Office has failed to articulate a reason with some rational underpinning to support its legal conclusion of obviousness for the reasons stated above

The Office response to these arguments is by picking and choosing elements from twelve references without reading each reference as a whole. The Office is not allowed to pick and choose the elements it likes while ignoring the rest of the reference. When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art).

For example, previously and reiterated herein, Applicants argue that none of the references discuss identifying a lymph node as a target for delivery of a protein and locating a site local to the lymph node. In response to this argument, the Office states that the argument "is not persuasive. Jolly teaches targeting lymph nodes." However, Jolly does not teach targeting lymph nodes in the same manner as the presently claimed invention. Jolly states,

> Other suitable packaging cell lines include the 293 2-3 VSV-G system, and cell lines that exhibit vector structural protein[s] modified to facilitate targeting of the transduction of the vector to a preferred location (e.g., a regional lymph node or a cell that presents a particular antigen).

(Jolly, Paragraph 0056). Jolly does not use the term "lymph node" anywhere else in the application. The Office takes the term "lymph node" completely out of context when it alleges that Jolly teaches targeting lymph nodes with a free DNA molecule. In contrast to the presently claimed invention Jolly at paragraph 0056 discusses the use of a packaging cell line to produce a vector. One of skilled in the art would understand that the use of the term "vector" in paragraph 0056 refers to a virus or pseudotype (*e.g.* virus like particle) that can be used to target a lymph node, not a free DNA molecule. Packaging cell lines are not used to produce free DNA molecules. Jolly discusses using a specific agent (virus or virus like particle) that specifically targets a lymph node because of its structure (*e.g.* surface proteins that can bind to lymph node cells). The agent in Jolly that is described paragraph 0056 has no structural similarity to a free DNA molecule or to the method where the free DNA molecule is administered to an individual proximal to a lymph node (*i.e.* not targeted directly to a lymph node) and taken up by a macrophage and then delivered to the lymph node. References must be read for what one of skill in the art would understand them to mean not just for the terms that it uses. "("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

The Office attempts to support the teachings of Jolly with Roitt, which allegedly teaches the circulation of macrophages through the circulatory system, to sites of injury and draining through the lymph node. However, one of skill in the art reading Jolly would not have used this pathway to target lymph nodes with a free DNA molecule in view of the foregoing. Applicants

have never argued that they identified for the first time that macrophages drain to the lymph system. The existence of the lymph system is only relevant to the extent that Applicants were the first to understand that it could be utilized as a highway to deliver proteins to a lymph node using a free DNA molecule. Prior to the present invention the prior art did not appreciate this fact and did not have a reasonable expectation of success that such a method would even work.

The Office also argues that the inclusion of Stacey remedies any deficiency the previous references had in showing that macrophages take up DNA and the macrophages drain to the lymph node. The Office has still not supported its conclusion with sufficient evidence to show that a free DNA molecule that is administered proximal to a lymph node will be taken up by a macrophage and delivered to the lymph node. As discussed above, Stacey discusses only *in vitro* experiments and Stacey admits that the mechanism may be different *in vivo*. Furthermore, the references still have not shown that one of skill in the art would have had a reasonable expectation of success that performing the presently claimed methods.

In response to Applicants' argument that the references do not disclose how to administer a free DNA molecule to a macrophage and that the references fail to disclose the step of identifying the lymph node and delivery by administering a DNA to a site that is local to the lymph node the Office uses an argument that does not even address the main point, that is the references fail to teach this element of the presently claimed invention. Instead the Office states that "the choice of a lymph node ***may*** be as broad as 'a lymph node in which muscle attracted macrophages drain', and hence all lymph nodes near muscle are identified." (Office Action, pages 9-10). Applicants respectfully disagree with this conclusion. There is nothing in the references where a lymph node is identified. The Office appears to be arguing that since lymph nodes are everywhere that they are identified just by existing. Existence of a lymph node is not the same as identifying a lymph node for delivery of a protein. Identifying a lymph node is an element of the claim and the existence of a lymph node is not enough to be equated with such an element.

The Office also alleges that

> "the choice of delivery to a specific lymph node would be that choice which is inherent in the method of choosing to deliver the

> protein to a specific lymph node. Because the Artisan knows the lymphatic system and that macrophages which migrate to tissues will then migrate to lymph nodes local to the site, the choice is obvious to the methods being performed."

(Office Action, page 10). Applicants respectfully disagree that the "choice" is inherent. The Office characterizes the choice as always using the lymphatic system. Applicants respectfully disagree with the characterization of the term "choice" as the Office is applying it to the presently claimed invention. The prior art does not disclose the entire method and it is not inherent to deliver a protein to a lymph node by the recited steps. The Office's allegation that these "choices" are inherent is not supported by the law or the facts of the present case. For a "choice" to be inherent the choice must always and necessarily flow from the reference. The references teach many "choices" for targeting a lymph node. For example, Jolly teaches the use of a vector to specifically target a lymph node and not even using a macrophage. (see, Jolly, paragraph 56). The Jolly "choice" is different from the presently claimed invention. Therefore, the choice, by definition, cannot be inherent since there are numerous methods, as evidenced by Jolly, to deliver a molecule to a lymph node.

In response to Applicants argument that Hedley is limited to subcutaneous injection and teaches away from the presently claimed invention, the Office responds that "Hedly is simply used to emphasize the teachings of Roitt." (Office Action, page 10). However, as discussed above, a portion of a reference cannot be read in isolation. A reference must be read as a whole and understood as one of skill in the art would understand the reference. Roitt does not cure the deficiencies of Hedley because Hedley on its own teaches away from the presently claimed invention. Roitt does not disprove Hedley or contradict it. In contrast, Hedley uses specific language that teaches away from the present invention, and therefore, cannot be used to show that the presently claimed methods are *prima facie* obvious.

The office also argues that Hedley does not teach away. The office states that "teaching away means that it disparages the other." The Office's interpretation of what constitutes "teaching away" is not correct. A reference teaches away when one of skill in the art after reading the reference "would be discouraged from following the path set out in the reference, or

would be led in a direction divergent from the path" disclosed in the reference. *In re Gurley* 31 U.S.P.Q.2d 1130, 1131 (Fed. Cir. 2004). Explaining further the court stated, "a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Id.* Here, Hedley discourages the use of a free DNA molecule because of its explicit differentiation between a free DNA molecule and the microparticle encapsulated DNA that is used.

In support of its argument that Hedley does not teach away the Office alleges that the scope of "free DNA" when given its broadest reasonable interpretation is broader than plasmids. Applicants agree that the interpretation can be broader than plasmids, however, a reasonable interpretation of a "free DNA molecule" does not include microparticle encapsulated DNA. One of skill in the art would not consider encapsulated DNA to be a free DNA molecule. If the Office maintains that a reasonable interpretation of a "free DNA molecule" includes DNA encapsulated by microparticles, Applicants respectfully request that such interpretation be supported by sufficient evidence of a declaration by the Examiner.

In contrast to the Office's interpretation of Hedley, when read as a whole, one reading Hedley would be discouraged from using anything other than DNA encapsulated by microparticles. Accordingly, Hedley teaches away from using the presently claimed method.

The Office also states that if "no one would choose a lymph node near the muscle, because the Artisan did not know if macrophages responded to muscle damage, and if they drained to lymph" that the claims would be allowable. (Office Action, page 11). Applicants respectfully assert that the Office is misinterpreting the argument and its understanding of the evidentiary burden that the Office is required to comply with in order to render claims *prima facie* obvious. Applicants previous responses were based upon the record put forward by the Office. The Office has admitted by withdrawing the previous rejection that the rejections were not proper. It is only now that the Office has found a reference discussing macrophage migration that the Office considers the rejection proper. However, the rejection is still improper because the Office has not shown that all of the references would have been combined to yield the presently claimed invention and provide a reasonable expectation of success.

Even though the Office has added seven new references to the obviousness rejection the combination still does not render the claims obvious for the reasons stated above. This present rejection is a classic example of where the Office has picked the elements that supports its argument and ignored the entirety of the document. Applicants respectfully remind the Office that hindsight reconstruction is strictly prohibited. Although many elements of the presently claimed method may have been known there was no suggestion or reason in the prior art to combine them all. The only argument that the Office has put forward is that each element exists in some form. For example, the Office alleges that Stacey discusses the uptake of DNA by macrophages. The Office, however, ignores the context of the Stacey paper where the uptake is in a completely artificial setting, which is significantly different from the presently claimed method.

Finally, the Office has failed to demonstrate that one of skill in the art would have had a reasonable expectation of success. The Office's rejection relies upon twelve references to show the claimed method. The combination still fails to yield the presently claimed method, but even if it did there is no reasonable expectation of success for the reasons discussed above.

The Office concludes that "proteins expressed from transfected cells at a damage site are delivered to the lymph nodes local to the site" and that this was known in the art and, therefore, the presently claimed invention is obvious. The Office fails to support this conclusion with sufficient evidence. The references, such as Stacey, may demonstrate that macrophage cells in a tissue culture dish can internalize DNA, but none of the references teach of suggest that after administration proximal to a lymph node a free DNA molecule will be internalized by macrophages *in vivo* and subsequently be delivered to the lymph node. The Office's rejection cannot be supported by mere conclusions. Although the references cited by the Office discuss various aspects of macrophages and the lymph system, none of the references alone or in combination yield the presently claimed invention.

Prior to the present invention it was not known or obvious that one could deliver a protein to a lymph node by the methods described in the pending claims. Here, applicants have shown that DNA injected intramuscularly is taken up by macrophage, which then travel to the lymph

node, whereupon the DNA is expressed to effectively deliver the protein to the lymph node. Applicants have shown that free DNA directly injected into an individual remains intact and functional such that when taken up by macrophage which travel to the lymph node, the DNA can be expressed to effectively deliver the protein to the lymph node. Those skilled in the art would not have expected these beneficial aspects in view of the combination of references. The cited references do not cure this deficiency that has been present in every obviousness rejection put forward by the Office since substantive examination has begun.

Accordingly, the claims are not obvious because the references do not support a finding that the claims are *prima facie* obvious, the references teach away from the presently claimed invention, and the reference fail to demonstrate that one of skill in the art would have an expectation of success. In view of the foregoing, Applicants request the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Claims 9, 15-16, 40-46 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7820 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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